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Hemodynamic Effects of Infused Arginine Vasopressin in Congestive Heart Failure

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The hemodynamic effects of exogenously administered arginine vasopressin were assessed in 11 patients with chronic congestive heart failure. Infusion rates of 0.1 to 0.8 pmol/kg per min increased plasma arginine vasopressin from 6.5 ± 2.7 (SD) pg/ml at control to 63 ± 39 pg/ml at the highest infusion rate. There were progressive decreases in cardiac output and stroke volume, with increases in systemic vascular resistance and pulmonary capillary wedge pressure, but only minimal changes in heart rate and blood pressure. Changes in cardiac output, stroke volume and systemic resistance were evident from the first infusion rate, which increased plasma arginine vasopressin from 6.5 ± 2.7 to 9.9 ± 4.6 pg/ml. A paired analysis of baseline hemodynamic data with those measured during infusions producing an arginine vasopressin level averaging 15 ± 2.6 pg/ml yielded the following changes: cardiac output decreased from 4.6 ± 1.2 to 4.2 ± 0.96 liters/min ($p < 0.01$), stroke volume decreased from 60 ± 19 to 54 ± 16 ml ($p < 0.005$) and systemic vascular resistance increased from 1,329 ± 396 to 1,443 ± 395 dynes·s·cm^{-5} ($p = 0.01$).

Thus, small increases in circulating arginine vasopressin cause modest but significant adverse circulatory effects in patients with congestive heart failure. A fall in cardiac output, probably as a result of increased afterload, is seen at levels of arginine vasopressin within the basal range found in congestive heart failure. These data demonstrate that circulating arginine vasopressin in physiologic concentrations is capable of influencing hemodynamics in patients with congestive heart failure and suggest that therapy for this condition directed at inhibition of the vascular effect of arginine vasopressin may be potentially useful.

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Arginine vasopressin, the human antidiuretic hormone, is a potent vasoconstrictor (1). Numerous studies (2–5) in the past several years have clearly demonstrated that it exerts important vascular effects at physiologic levels both in normal animals and in animals under a variety of types of stress. We have been interested in a possible role for arginine vasopressin in the vasoconstriction of human congestive heart failure because this condition frequently is characterized by elevated peripheral vascular resistance and activation of other neuroendocrine vasoconstricting systems (6,7). We (8) and others (9–12) have now shown that plasma arginine vasopressin levels tend either to be increased or to be inadequately suppressed for the prevailing plasma osmolality in patients with heart failure. The current study was performed to address the issue of whether physiologically relevant concentrations of plasma arginine vasopressin can exert important hemodynamic effects in patients with this condition.

Methods

Study patients. Eleven patients with chronic congestive heart failure (New York Heart Association functional classes II to IV) formed the study group for this investigation. All were receiving digitalis and diuretic drugs and most had been treated with vasodilating drugs. Patients were always studied in a stable clinical state with diuretics and vasodilators discontinued at least 12 hours in advance. The patients' ages ranged from 20 to 74 years (mean 53); 10 were men. Three had ischemic cardiomyopathy documented by a history of myocardial infarction or coronary angiography, and eight had idiopathic dilated cardiomyopathy. All had

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well documented depressed ventricular function by angiographic, echocardiographic or radionuclide studies.

Protocol. After giving informed consent, all patients had a Swan-Ganz catheter inserted through either the median basilic or femoral vein. A short cannula was also placed in a brachial or femoral artery. At least 30 minutes was allowed to pass before baseline hemodynamic measurements were begun. These were repeated at 5 minute intervals and, if stable for at least two determinations, were accepted as basal. Blood was then drawn for plasma arginine vasopressin analysis and placed immediately into chilled tubes. An infusion of synthetic arginine vasopressin (Pitressin, Roche Pharmaceuticals) was then begun at 0.1 pmol/kg per min. The infusion was prepared by mixing 10 units of Pitressin in 250 cc of 5% dextrose in distilled water. Four microdrops per minute provided the starting infusion rate for an average-sized subject. The infusion was maintained for 10 minutes, after which hemodynamic measurements were repeated and blood was drawn again for arginine vasopressin determination. The infusion rate was then increased to 0.2, 0.4 and 0.8 pmol/kg per min with hemodynamics assessed and blood samples taken at each infusion rate as during the first infusion rate. No subject experienced any reactions during the study or was aware of any clinical changes.

Data analysis. Data were analyzed by analysis of variance for repeated measures on the same elements. If significant variation was observed, the data from each infusion rate were compared with control data using a paired *t* test with Bonferroni's correction. Because of wide standard deviations for the actual arginine vasopressin levels achieved during the infusions, particularly at the last two infusion rates, a paired analysis was also carried out for each variable at the control level and at the infusion rate producing plasma arginine vasopressin levels between 10 and 20 pg/ml in each individual subject. This procedure was followed because our primary objective was to establish whether levels of arginine vasopressin within the range observed for basal values in heart failure were capable of exerting hemodynamic effects in this condition.

Plasma was separated by cold centrifugation within 2 hours after blood sampling and immediately frozen at −20°C for later analysis. Samples were always extracted and analyzed within 60 days. Analysis was carried out as previously described by a sensitive and specific radioimmunoassay (13). Current inter- and intraassay coefficients of variation average approximately 8%.

Results

The basal arginine vasopressin level in this group of patients was 6.4 ± 2.7 (SD) pg/ml, which is higher than our average normal value of 4.7 ± 2.4 pg/ml in middle-aged subjects but lower than the mean level of 9.5 ± 4.1 pg/ml we previously reported in a larger group of patients with heart failure.

Hemodynamic results. Figure 1 plots the results for each hemodynamic variable at each infusion rate. The corresponding arginine vasopressin levels (pg/ml) achieved for each infusion rate were as follows: 0.1 pmol/kg per min, 9.9 ± 4.6; 0.2 pmol/kg per min, 18.3 ± 10; 0.4 pmol/kg per min, 34.6 ± 24; and 0.8 pmol/kg per min, 63 ± 39. During the infusion, heart rate and blood pressure did not change except for a small increase in blood pressure at the highest rate. Cardiac output (liters/min) declined from 4.6 ± 1.2 to 4.2 ± 1.3 ($p = 0.012$) during the first infusion period, was relatively stable at 4.1 ± 1.1 during the second period and declined further ($p < 0.01$) during the last two infusion periods (to 3.8 ± 0.9). Stroke volume (ml) declined from 60 ± 19 to 55 ± 20 ($p = 0.02$) at the first infusion rate, remained relatively stable (54 ± 17) at the second and declined further ($p < 0.01$) to 51 ± 17 at the higher rates. Systemic vascular resistance (dynes·s·cm^{-5}) increased from 1,329 ± 397 at control to 1,445 ± 440 ($p = 0.012$) during the first infusion rate, was again stable during the second infusion rate (1,457 ± 390) and increased further to 1,524 ± 452 and 1,578 ± 477 during the final infusion periods. There was significant overall variation ($p < 0.01$) in the pulmonary wedge pressures, but no individual pairs attained statistical significance with the corrected *t* tests. There was no change in right atrial pressure and pulmonary artery pressure remained stable.

As discussed, because of some variability in the actual arginine vasopressin levels achieved at each rate, we also analyzed in a paired fashion the control data and those from the arginine vasopressin infusion rate producing a plasma level of between 10 and 20 pg/ml (mean 15 ± 2.6). Individual responses from this analysis are shown in Figure 2. There were small but significant increases in systemic vascular resistance (1,329 ± 396 to 1,443 ± 395 dynes·s·cm^{-5}, $p < 0.01$), decreases in cardiac output (4.5 ± 1.2 to 4.2 ± 0.9 liters/min, $p < 0.01$) and decreases in stroke volume (60 ± 19 to 54 ± 16 ml, $p < 0.001$). The increase in pulmonary capillary wedge pressure (22 ± 6.9 to 23 ± 6.3 mm Hg) was not statistically significant. Heart rate and blood pressure were unchanged.

Discussion

Adverse hemodynamic effects of increased plasma arginine vasopressin. The data from this study demonstrate adverse circulatory effects from increases in plasma arginine vasopressin in patients with congestive heart failure. Inspection of the data from the two lowest infusion rates shows that adverse effects occurred with very small increases in arginine vasopressin over baseline. Analysis of baseline data

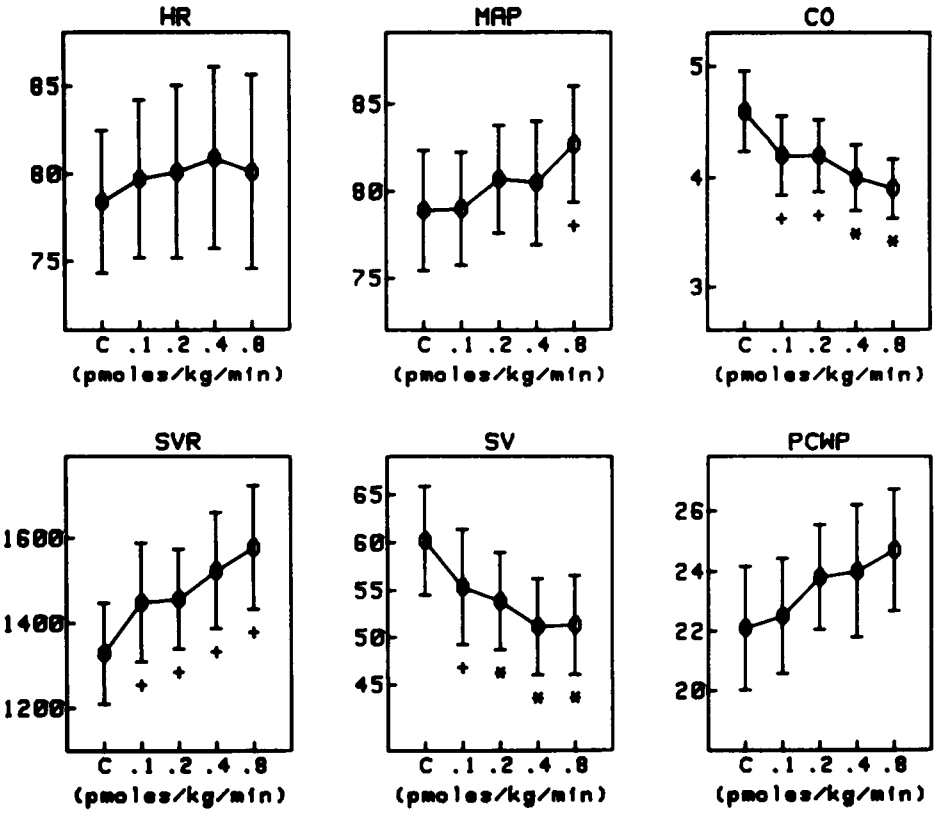

Figure 1. Overall hemodynamic responses to arginine vasopressin infusions. Data are shown as mean ± SD for each infusion rate. See text for the arginine vasopressin levels corresponding to the infusion rate. $^{+}p < 0.05$; $^{*}p < 0.01$. CO = cardiac output (liters/min); HR = heart rate (beats/min); MAP = mean arterial pressure (mm Hg); PCWP = pulmonary capillary wedge pressure (mm Hg); SV = stroke volume (ml); SVR = systemic vascular resistance (dynes·s·cm^{-5}).

and those during an arginine vasopressin level between 10 and 20 pg/ml in all subjects confirmed these effects (Fig. 2). The major hemodynamic changes seen were a decrease in cardiac output due entirely to a fall in stroke volume and an increase in systemic vascular resistance. Arginine vasopressin is not thought to exert major primary effects on myocardial function (14); hence, although we cannot exclude direct cardiodepression, the deterioration in cardiac output was probably a consequence of the enhanced sensitivity of the abnormal ventricle to peripheral vasoconstriction. There were also smaller but still consistent increases in the pulmonary capillary wedge pressure. We cannot exclude an effect due to coronary vasoconstriction with impaired left ventricular function secondary to ischemia, but most of the patients had no known coronary artery disease, none reported chest discomfort and the changes in pulmonary capillary wedge pressure were quite modest. These factors, plus the absence of heart rate and blood pressure changes, argue against ischemia-induced cardiodepression and in favor of a decrease in function secondary to afterload stress alone or in combination with direct cardiodepression.

Neurohumoral effects of arginine vasopressin. Arginine vasopressin is a potent direct vasoconstrictor (1) and also may potentiate the vasoconstricting effects of norepinephrine and angiotensin II (15,16). We did not measure norepinephrine and renin levels in these patients, but because these neurohumoral controllers are also frequently increased in patients with heart failure (6,7), some of the vasoconstricting effects of arginine vasopressin seen in this study could have been a result of an interaction of arginine vasopressin with these other neurohumoral mediators. Such potentiating effects have been observed in animals with changes in arginine vasopressin as small as 1 pg/ml (15,16). Therefore, very small changes in plasma arginine vasopressin, even if not exerting independent effects, may be important in a milieu of overall increases in neurohumoral activity coupled with extreme sensitivity of ventricular function to afterload stress such as is found in congestive heart failure. Further study to examine the interactions of arginine vasopressin, norepinephrine and angiotensin II seems warranted in patients with this disease.

Effect on cardiac output. As noted, the decrease in cardiac output in these patients was due to a fall in stroke volume, heart rate having remained stable. Cardiac output does fall in normal animals given small amounts of arginine vasopressin, but the fall is due almost entirely to a decrease in heart rate caused by an interaction between arginine vasopressin and the sinoaortic baroreceptors (14). Similar data have been reported in preliminary form in normal humans, albeit with noninvasive cardiac output determinations (17). The observation of depressed cardiac output during low level arginine vasopressin infusions may therefore not be unique to congestive failure, but the mechanism is different, because in heart failure the decreased output occurs indepen-

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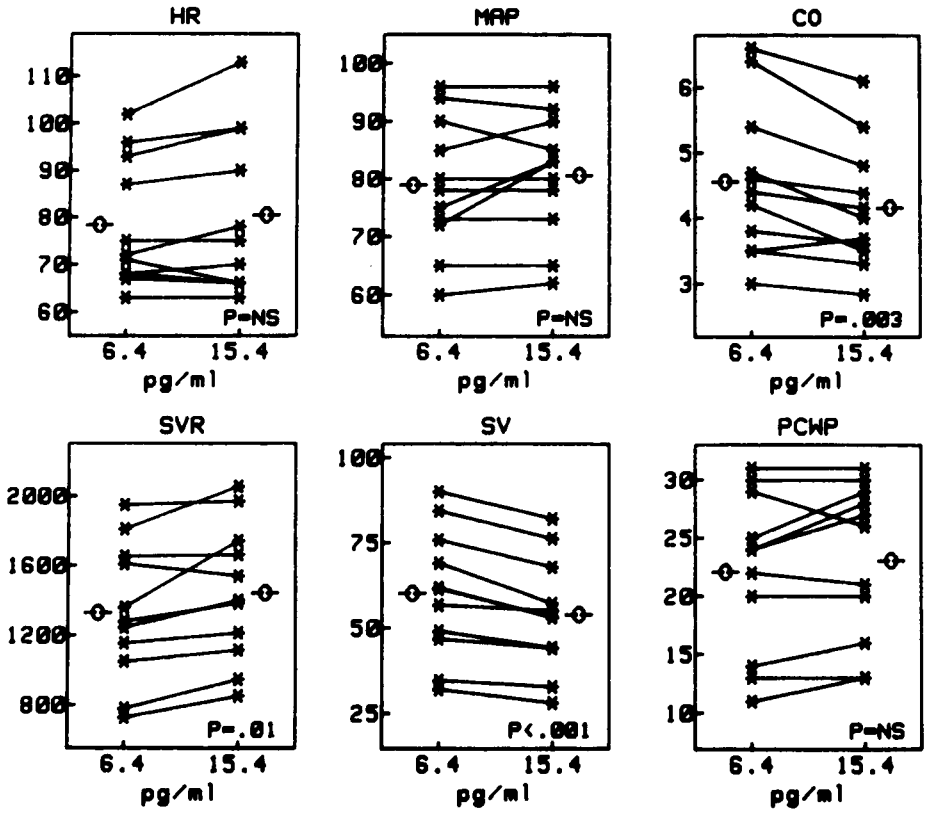

Figure 2. Individual hemodynamic responses to arginine vasopressin infusions in 11 patients. The control hemodynamic measurements are compared with those from the infusion rate increasing the arginine vasopressin level from control levels to between 10 and 20 pg/ml for each individual patient. The p value is that from a paired *t* test. Abbreviations as in Figure 1.

dent of heart rate. The lack of heart rate depression in congestive failure could be a result of blunted sinoaortic baroreceptor function in this condition.

Potential limitations. We believe that the hemodynamic changes observed in this investigation are not likely to have been due to factors other than the arginine vasopressin infusions. Hemodynamic variables were stable before the infusion, volumes of fluid administered were very small, no subject reported adverse reactions and the absence of heart rate and blood pressure changes argues against any spontaneous stress-induced cardiovascular impairment. It has also recently been observed that the hemodynamic status spontaneously improves, rather than worsens, after right heart catheterization without further intervention in congestive heart failure (18), so it is possible that we may even have underestimated the effects of vasopressin. Finally, we should note that the responses to arginine vasopressin were remarkably consistent despite a fairly wide range of baseline hemodynamics (Fig. 2). Given these considerations, we believe we were in fact observing the effects of the arginine vasopressin infusion and not those of chance or other variables.

Clinical implications. A clear implication of our study is the possibility that arginine vasopressin may participate in the vasoconstriction of congestive heart failure. Our data do not permit speculation about the role of arginine vasopressin in the baseline vasoconstriction of congestive heart failure, because we cannot extrapolate from the effects of an increase in circulating arginine vasopressin to the basal state. However, we have shown that very small increases in arginine vasopressin over baseline (from 6.4 ± 2.7 to as little as 9.9 ± 4.0 and 18.3 ± 10 pg/ml) (Fig. 1) can exert definite, if modest, hemodynamic effects. Most current studies on arginine vasopressin in heart failure have been performed under basal conditions in stable patients, whereas few data are available concerning arginine vasopressin levels during clinical decompensation or osmotic stimulation in heart failure. Eleven patients in our original series had arginine vasopressin levels between 10 and 20 pg/ml, and two had levels over 20 pg/ml. Riegger et al. (19) recently reported on a group of sicker patients in whom plasma arginine vasopressin averaged over 40 pg/ml. Arginine vasopressin increases markedly (to levels of 80 pg/ml or more) during hypotension in normal subjects (20). We have reported that arginine vasopressin is stimulated by acute furosemide administration in heart failure (21) and Uretsky et al. (12) reported striking increases in arginine vasopressin during osmotic stimulation in patients with heart failure. Hence, it is clear that the levels produced during our infusion study are well within the observable range in clinical congestive heart failure.

Therapeutic implications. To fully clarify the role of arginine vasopressin in the vasoconstriction of congestive heart failure, studies with selective inhibitors of the vascular effects of arginine vasopressin are needed, under both normal and stressed conditions. Relatively selective blockers

of the "V_1" or vascular receptor for arginine vasopressin are now available (22). The first report in subjects with heart failure demonstrated no effect of such a blocker if arginine vasopressin levels were normal, but a dramatic vasodilating response in one subject with high arginine vasopressin levels (23). A second report (24) using this compound indicates possible partial agonist effects at low arginine vasopressin levels yet demonstrated vasodilation in three subjects with increased levels. The infusion data from our study therefore complement these preliminary inhibitor trials by demonstrating vasoconstricting effects of modest increases in arginine vasopressin in congestive heart failure. On the basis of all current data, we believe that continued evaluation of arginine vasopressin blockade in patients with congestive heart failure may be warranted. It is possible, with the renin-angiotensin system and converting enzyme inhibition as a precedent, that targeted therapy at arginine vasopressin-mediated vasoconstriction might prove to be another step in the rational design of specific vasodilator therapy for some patients with this disease.

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